

# Prokinetic drugs for feed intolerance in critical illness: current and potential therapies

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Enteral nutrition is the preferred method of feeding critically ill patients.<sup>1</sup> However, nutritional goals are frequently not met via the gastric route because of abnormal gastrointestinal motility, which causes delayed gastric emptying<sup>2</sup> (Table 1). This is characterised by a slowing of the chyme flow velocity into the duodenum, resulting in retained gastric contents, and has been demonstrated in critical illness by a variety of techniques, including scintigraphy (Figure 1), paracetamol absorption and breath tests.<sup>3-7</sup>

As formal measurement of gastric emptying is not practical in the intensive care unit, a surrogate measurement — gastric residual volume (GRV) — is often used.<sup>8</sup> Although an association between the two is likely, the accuracy of GRV for predicting delayed gastric emptying depends on the threshold volume chosen.<sup>9</sup> Furthermore, larger GRVs are likely to reliably predict delayed gastric emptying, but the sensitivity of GRV will always be limited by the inaccuracy of the test (ie, the inability to predictably and reliably empty the stomach).<sup>9,10</sup>

Feeding protocols usually incorporate intermittent aspiration of gastric contents, although algorithms vary in the volume used to indicate “feed intolerance” and the subsequent actions recommended.<sup>10</sup> Large GRVs may be treated by any of the following:

- returning some or all of the gastric contents;
- reducing the rate of nutrient administration; and
- prokinetic therapy (Figure 2).

In patients with large GRVs, a reduction in feed rate is sometimes recommended because of a perceived risk of aspiration of gastric contents. It is presumed that delayed gastric emptying and gastric distension increase the frequency and volume of gastro-oesophageal reflux and aspiration. However, studies in both ambulant humans and critically ill patients have failed to confirm an association between delayed gastric emptying and gastro-oesophageal reflux,<sup>11</sup> or feed intolerance and aspiration,<sup>12</sup> and protocols that recommend a reduction in feed rate risk delivering insufficient nutrients. An alternative strategy is to treat a large GRV immediately with an effective prokinetic regimen,<sup>13</sup> with any subsequent large GRV treated with prompt insertion of a postpyloric tube.<sup>13</sup> It may then be possible to avoid reducing feed rates, and the attendant risk of inadequate nutrition.

Outside the ICU, important outcome measures in studies of prokinetic therapies are the effect on upper gastrointesti-

## ABSTRACT

Studies consistently show that nasogastric nutrition delivers only about 60% of nutritional goals in critically ill patients. The predominant reason is abnormal gastric motility, leading to delayed gastric emptying, which is evident clinically as large gastric residual volumes. Delayed gastric emptying occurs in about 50%–60% of critically ill patients who are fed enterally and can result in malnutrition. Furthermore, delayed gastric emptying may increase the risk of aspiration of gastric contents. Recent research has improved our understanding of the complex abnormalities of gastric motor function that underlie delayed gastric emptying in the critically ill. Feed intolerance can be treated with prokinetic drugs and/or by the placement of postpyloric feeding catheters. The place of prokinetic agents in the treatment of feed intolerance is as yet unclear, but current evidence supports the administration of erythromycin combined with metoclopramide as first-line therapy. Other novel drugs, such as methylnaltrexone, mitemincin, ghrelin agonists and dexloxiglumide, have potential advantages over these agents but require further investigation before widespread clinical use.

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nal symptoms and gastric emptying. In contrast, in sedated critically ill patients, symptom relief is far less important, and the outcomes of primary interest are feed tolerance and gastric emptying. Symptomatic improvement in ambulant patients (due to accelerated gastric emptying) may not equate to improved feed tolerance in the critically ill.

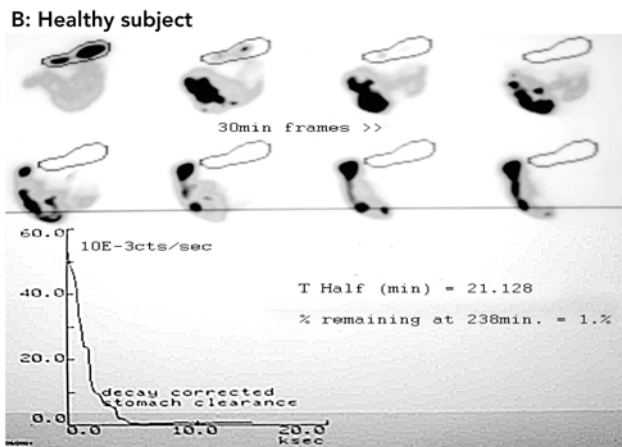
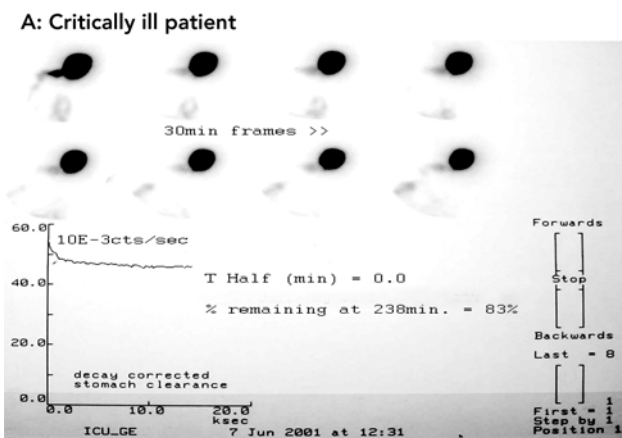
## Mechanism of liquid gastric emptying in health

Gastrointestinal motor activity is broadly divided into fasting and postprandial patterns. The postprandial period is initiated by nutrient intake and, by definition, ends with the recurrence of fasting motility, recognised by the appearance of phase III of the migrating motor complex in the upper small bowel.<sup>14</sup> Postprandial motility patterns differ depending on whether the nutrient is solid or liquid, but the activity results in breakdown, digestion and distal transfer of nutrients. While fasting motility has a role in normal

**Table 1. Definitions**

*Delayed gastric emptying:* Disordered gastric motility leading to slowing of the flow of gastric contents into the duodenum.  
*Feed intolerance:* An inability to reach or maintain the targeted rate of feed delivery during enteral nutrition. The most common limiting factor is a large gastric residual volume. Feed-intolerant patients are more likely to have delayed gastric emptying.

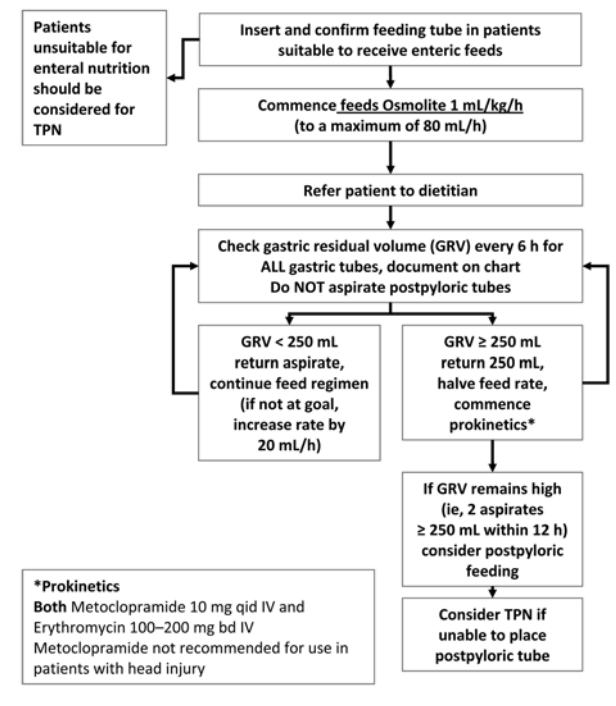
**Figure 1. Scintigraphic measurement of gastric emptying in a critically ill patient and a healthy subject**



Images acquired over time show that emptying of liquid nutrient occurs rapidly in health (bottom sequence), but is delayed in critical illness (top sequence). In addition, the magnitude of gastroparesis that occurs in critical illness can be appreciated by the significant volume of feed retained in the stomach at study end ( $t=238$  minutes).

physiology, the usual feeding regimens in critically ill patients use continuous infusion. Hence, knowledge of luminal motor patterns during fasting is less relevant, while an understanding of liquid nutrient gastric emptying is required.

**Figure 2. Current protocol used to guide nutritional therapy in the critically ill at the Royal Adelaide Hospital**

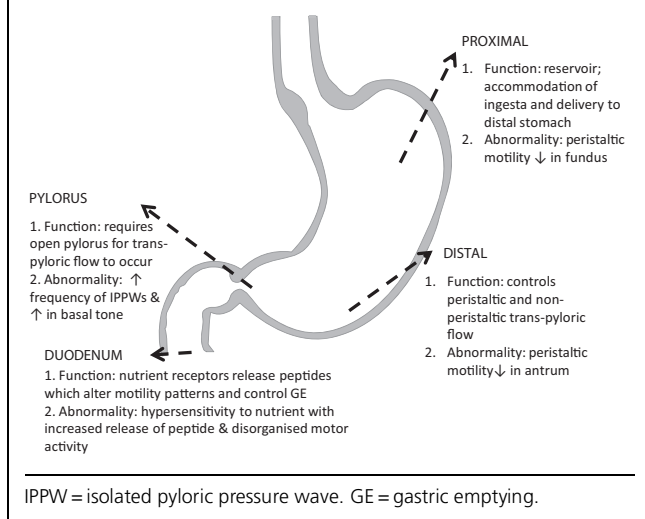


TPN = total parenteral nutrition.

By convention, the stomach is separated into distinct regions: the proximal (fundal), and distal (antral and pyloric) regions. Evidence is contradictory about the importance of each region to gastric emptying of liquids. Some experts believe the proximal region to be more significant,<sup>15</sup> while others maintain the distal region is more important.<sup>16</sup> However, neither area functions in isolation,<sup>17</sup> and impaired gastric emptying usually involves a disordered and poorly integrated response throughout the entire stomach.<sup>18</sup> Following ingestion of liquids, the proximal stomach acts as a reservoir, with inhibition of tonic contraction of the gastric smooth muscle. The resulting relaxation of the proximal stomach allows filling with ingesta with only minor increases in pressure. Gastric accommodation may be prolonged (up to 3 hours) and persists until emptying is almost complete.<sup>19</sup> The function of the proximal stomach includes fundal pressure waves, which assist aboral movement of the ingesta.<sup>20</sup>

The distal stomach is largely responsible for emptying, with coordinated antral and pyloric motility facilitating flow of chyme into the proximal duodenum. Transpyloric flow requires the generation of a transpyloric pressure gradient, which occurs during both peristaltic and non-peristaltic gastric motor activity.<sup>21,22</sup> During peristaltic flow, organised

**Figure 3. Function and abnormalities of the various regions of the stomach in critically ill patients**



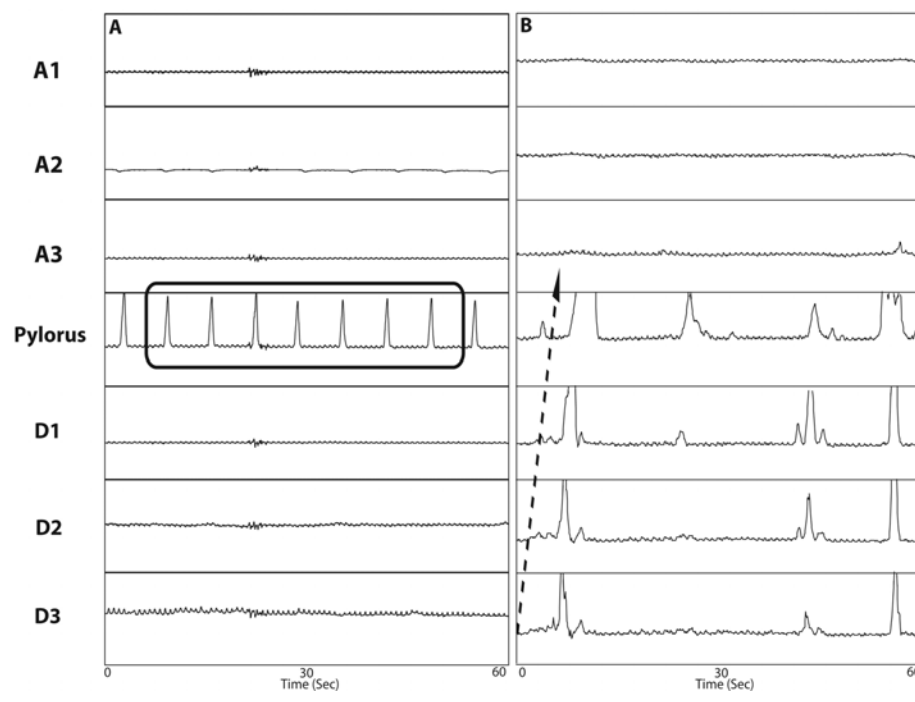
tric emptying of nutrient is thus limited; for example, emptying of a glucose solution is limited to 2–3k cal/min (8.4–12.5 kJ/min).<sup>30</sup>

**Abnormal motility and delayed gastric emptying in critical illness**

Disturbances in both proximal and distal gastric motor patterns have been described in critically ill patients with delayed gastric emptying.<sup>31–34</sup> In the proximal stomach, decreased frequency and amplitude of fundic waves, along with loss of recovery of tone, are postulated to reduce movement of nutrient to the distal stomach.<sup>32</sup> In the distal stomach, transpyloric flow is impaired by a reduction in frequency and amplitude of antral contractions, along with an increase in pyloric tone and the number of isolated pyloric pressure waves.<sup>31</sup> The mechanism for disordered gastric motility appears to be hypersensitivity to the presence of nutrient in the small intestinal lumen.<sup>31</sup> An enhanced neuro-

waves of muscle contractions commence in the antrum and propagate distally through the pylorus and into the duodenum,<sup>23</sup> with the antral contractions stimulated by the presence of volume or nutrient in the stomach.<sup>24</sup> Non-peristaltic flow occurs through the generation of a gastric–duodenal pressure gradient across an open pylorus.<sup>25</sup> Animal studies report that pyloric relaxation is under both extrinsic (via the vagus nerve)<sup>26</sup> and enteric neural control.<sup>27</sup> However, to retard gastric emptying and limit duodenogastric reflux, prolonged periods of pyloric closure are needed.<sup>28</sup> Isolated pyloric pressure waves reflect phasic contractions localised to the pylorus and often associated with an increase in pyloric tone. Together, these phasic and tonic changes reduce transpyloric flow.<sup>29</sup> Mechanical, chemical and osmolar stimulation in the duodenum is responsible for activating the ascending excitatory motor pathways to the pylorus, thereby slowing gastric emptying by a feedback mechanism. Gas-

**Figure 4. Manometric recordings of pressure waves in the gastric antrum and duodenum of a critically ill patient during small intestinal nutrient infusion**



Pressure waves in the antral (A1–A3), pyloric and duodenal (D1–D3) channels. Both traces show an absence of antral activity. **Panel A** shows isolated pyloric pressure waves, a motility pattern associated with cessation of transpyloric flow. **Panel B** shows retrograde motor activity originating in the duodenum (dotted arrow), which may push duodenal contents back into the stomach. Both these motility patterns are likely to delay gastric emptying and cause feed intolerance.

**Table 2. Characteristics of current and potential prokinetic drugs**

Drug	Parenteral formulation	Dosage	Mechanism of action	Action in critically ill patients
Metoclopramide	Yes	10–20 mg IV, 4–6-hourly	Dopamine (D <sub>2</sub> ) antagonist, 5-HT <sub>3</sub> receptor antagonist, 5-HT <sub>4</sub> agonist, indirect cholinergic	Enteral administration ineffective. IV administration accelerates gastric emptying in a mixed group, but ineffective in patients with TBI. No effect on GRV
Erythromycin	Yes	200 mg IV, 12-hourly	Motilin agonist	Increases antral activity and accelerates gastric emptying
Naloxone	Yes (but should be given enterally for this indication)	8 mg, 6-hourly	Opiate antagonist	Reduces GRV and incidence of ventilator-associated pneumonia
Alvimopan	No	6 mg, 12-hourly	Opiate antagonist	No data
Mitemincin	No	10–30 mg, 12-hourly	Motilin agonist without antibacterial activity	No data
Domperidone	No	10–20 mg, 6-hourly	Dopamine (D <sub>2</sub> ) antagonist	No data
Ghrelin	Yes	10 pmol/kg/min infusion	Ghrelin receptors	No data
Dexloiglumide	No	200 mg, 8-hourly	CCK receptor antagonist	No data
Tegaserod	No	6 mg, 12-hourly	5-HT <sub>4</sub> receptor partial agonist	Decreases GRV; no longer available because of adverse events
Neostigmine	Yes	2 mg IV or 0.4–0.8 mg/h infusion	Cholinergic	Underpowered study; trend to improvement in gastric emptying and reduced GRV

IV = intravenous. 5-HT = 5-hydroxytryptamine. TBI = traumatic brain injury. GRV = gastric residual volume. CCK = cholecystokinin.

humoral feedback loop has been demonstrated, mediated principally by cholecystokinin and Peptide YY.<sup>35</sup> A further impediment to gastric emptying is retrograde duodenal motor contractions,<sup>34</sup> which may cause chyme boluses to regurgitate into the stomach (Figure 3 and Figure 4).

**The ideal prokinetic drug**

The ideal prokinetic drug would increase fundal tone and pressure wave frequency, stimulate antral wave amplitude and frequency, reduce pyloric wave frequency and abolish pyloric tone. The propagation and integration of the resulting gastroduodenal motor pattern would ensure antegrade movement of chyme. However, acceleration of gastric emptying should not affect intestinal transit nor impair nutrient absorption. Furthermore, the ideal agent would optimise colonic function, facilitating normal bowel actions without causing diarrhoea. Importantly, the drug should not have adverse effects. It should also remain effective despite continued use, as current therapies are limited by tachyphylaxis.<sup>36–38</sup> It would also be desirable for the drug to have a wide therapeutic index and limited interaction with other drugs, and for its metabolism to be unaffected by liver or kidney impairment. No current agent meets all these criteria; current and potential prokinetic drugs are summarised in Table 2.

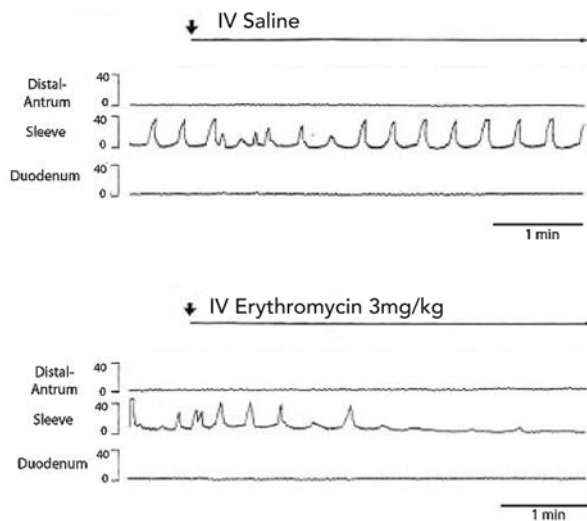
**Current prokinetic drugs**

**Metoclopramide**

Metoclopramide is a commonly used antiemetic and prokinetic with complex actions. It acts predominantly as a dopamine (D<sub>2</sub> receptor) antagonist with both central and peripheral effects. In addition, it has weak mixed serotonergic effects, with partial antagonism of 5-hydroxytryptamine (5-HT)<sub>3</sub> and agonism of 5HT<sub>4</sub> receptors. The motility effect is due to dopamine antagonism and peripheral 5HT<sub>4</sub> agonism.<sup>39</sup> In non-critically ill patients with gastroparesis, metoclopramide accelerates gastric emptying by triggering an intense burst of gastric contractions.<sup>40</sup> However, the long-term benefits on gastric emptying are uncertain, as tachyphylaxis is reported in diabetic patients with gastroparesis.<sup>36</sup>

Metoclopramide is widely used as a prokinetic in the management of feeding in critically ill patients, but recent studies have shown only a moderate prokinetic effect, which is limited by rapid tolerance.<sup>37</sup> The drug can be given by the enteral or parenteral route. Two studies examining the effect of metoclopramide given enterally were limited by design and lack of power, and produced conflicting results.<sup>41,42</sup> The effect of enteral metoclopramide in the critically ill therefore remains uncertain. Two small crossover studies examining the effect of intravenous metoclopramide in critically ill patients have also reported inconsistent results. One study enrolled unselected ICU patients,<sup>43</sup> and

**Figure 5. Pyloric motility during intravenous infusion of saline and erythromycin**



*Example of abolition of phasic and tonic pyloric motility by intravenous (IV) infusion of erythromycin (3mg/kg). IV saline had no effect on pyloric phasic and tonic motility, while phasic contractions were rapidly abolished by IV erythromycin. Following this there was a marked stimulation of gastroduodenal motility (see Figure 6).*

the other, patients with traumatic brain injury.<sup>44</sup> Jooste and others reported acceleration of gastric emptying with metoclopramide given to a mixed group of critically ill patients,<sup>43</sup> although there was no reduction in observed GRV. In contrast, metoclopramide did not accelerate gastric emptying in patients with traumatic brain injury,<sup>44</sup> although the drug effect may have been attenuated by a significant crossover effect. In the largest and most recent study, intravenous metoclopramide (10 mg four times daily) was compared with erythromycin (200 mg twice daily) in 90 critically ill patients who were intolerant of nasogastric feeds: 62% of patients who received metoclopramide tolerated feeding on Day 1, but only 16% remained feed-tolerant by Day 7.<sup>37</sup>

If metoclopramide accelerates gastric emptying in the critically ill, therapy could potentially reduce the prevalence of ventilator-associated pneumonia. However, Yavagal and colleagues randomly allocated 305 patients to receive 10 mg metoclopramide enterally every 8 hours or placebo for the duration of their ICU admission, finding that the therapy did not prevent ventilator-associated pneumonia.<sup>45</sup>

In non-critically ill patients, central nervous system adverse effects occur in up to 20% of subjects.<sup>46</sup> Symptoms include drowsiness, agitation and extrapyramidal effects.<sup>46</sup> Most of these symptoms would be difficult to detect in sedated patients. While movement disorders could impede

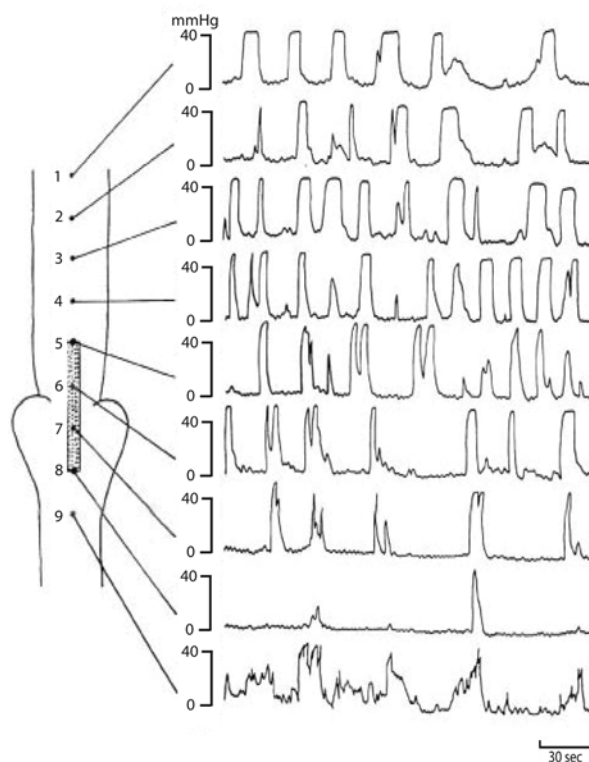
weaning from mechanical ventilation, metoclopramide-induced movement disorders have not been reported. However, metoclopramide was reported to raise intracranial pressure in a patient with head injury.<sup>47</sup>

Metoclopramide thus appears to have a limited role in the treatment of delayed gastric emptying. When given intravenously, it has a small, but measurable, prokinetic effect; however, this is limited by the rapid development of tachyphylaxis. In patients with traumatic brain injury, metoclopramide appears to be ineffective and may have significant adverse effects, and thus cannot be recommended on the current available evidence.

### Erythromycin

Macrolide antibiotics such as erythromycin act as competitive agonists of motilin. Motilin receptors are found predominantly in gastric antrum smooth muscle and proximal duodenum,<sup>48</sup> and when stimulated induce isolated contractions of smooth muscle.<sup>49</sup> At lower concentrations, erythro-

**Figure 6. Peristaltic activity in the stomach and duodenum after intravenous infusion of erythromycin**



*Erythromycin (3mg/kg) induces antral activity (traces 1-4), which propagates in an antegrade fashion into the duodenum (trace 9). This motor pattern has been associated with rapid gastric emptying.*

mycin also has a chronotropic effect mediated by neuronal motilin receptors.<sup>49</sup> Erythromycin increases the coordination of antroduodenal motility by stimulating antral activity and abolishing isolated pyloric pressure waves<sup>50</sup> — motor effects that would be expected to accelerate gastric emptying.

The effect of erythromycin on gastric motor activity is dose-dependent,<sup>51</sup> and the dosage of erythromycin required to accelerate gastric emptying is less than that required for its antibacterial action. Very low doses of erythromycin (40 mg) have different effects on motility compared with moderate doses (200 mg or 350 mg).<sup>52-54</sup> In healthy volunteers and patients with diabetic gastroparesis, 40 mg erythromycin infused intravenously induced premature antral phase III activity, which migrated to the small intestine.<sup>53,54</sup> At moderate doses (200–350 mg), erythromycin induced prolonged periods of stronger and more frequent antral contraction,<sup>52,54</sup> and reduced the frequency of pyloric pressure waves and abolished pyloric tone<sup>50</sup> — motor patterns which are likely to accelerate gastric emptying very efficiently (Figure 5 and Figure 6). Still higher doses (500 mg to 1 g — antibiotic dosage) of erythromycin induces strong antral contractions, although the activity is associated with upper abdominal pain and nausea.<sup>55</sup>

The prokinetic effects of erythromycin have been extensively investigated, particularly in patients with diabetic gastroparesis.<sup>56</sup> It accelerates gastric emptying in diabetic gastroparesis refractory to other prokinetics,<sup>57-59</sup> after gastric and non-gastric surgery,<sup>60,61</sup> and in anorexia nervosa<sup>62</sup> and progressive systemic sclerosis.<sup>63</sup> Long-term use is associated with some attenuation of effect.<sup>56,64</sup> It has also been administered preoperatively, to provide an empty stomach before anaesthesia.<sup>65</sup>

Erythromycin increases antral motility and accelerates gastric emptying in unselected critically ill patients.<sup>66</sup> A single 200 mg dose improves the success of feeding,<sup>67</sup> and following repeated dosing has a superior prokinetic effect to metoclopramide.<sup>37,68</sup> However, there is significant attenuation of effect, such that at the end of a week of therapy only about 35% of patients continue to tolerate nasogastric feeding.<sup>37,38</sup> Seventy milligrams of erythromycin has been shown to accelerate gastric emptying as effectively as 200 mg, and the use of a smaller dose may reduce the risk of adverse effects.<sup>69</sup> Erythromycin may also have a role in facilitating transpyloric placement of feeding tubes.<sup>70-74</sup>

Hyperglycaemia and a requirement for catecholamines are both common in critical illness. Both are known to slow gastric emptying, and may obscure the effects of erythromycin on gastrointestinal motility. Barnert and others reported a diminished effect of erythromycin on gastric emptying and gastroduodenal motility in the presence of high-dose catecholamines.<sup>75</sup> Similarly, erythromycin-induced acceleration of gastric emptying of hypertonic

liquids in patients with diabetes was reduced by hyperglycaemia.<sup>76</sup> There are thus features of critical illness that may reduce the prokinetic effect of erythromycin.

Enthusiasm for the use of erythromycin is tempered by fears of cardiac toxicity and bacterial resistance.<sup>77,78</sup> Erythromycin has been reported to prolong the QT interval, possibly through a direct effect on motilin receptors.<sup>79</sup> Potentially fatal ventricular arrhythmias can occur, particularly when erythromycin is used in combination with other drugs that affect the electrophysiology of cardiac muscle. Cardiac toxicity can be minimised by using the lowest effective dose.

The potential to induce antibiotic resistance remains a concern.<sup>78</sup> Macrolides have time-dependent antibacterial activity, and the use of low doses at less frequent intervals is likely to encourage bacterial resistance. However, the risk remains theoretical, as there is no evidence to confirm that erythromycin has altered bacterial resistance patterns within the ICU, and an audit of our practice found that the vast majority of prokinetic therapy is prescribed in patients who are receiving therapeutic doses of antibiotics for other indications (unpublished data). However, ongoing vigilance for emerging resistance patterns is required, and the development and investigation of motilin agonists that lack an antibiotic effect is warranted.

The impact of drug interactions with erythromycin in critically ill patients is unknown. Erythromycin inhibits the cytochrome P450-3A4 enzyme.<sup>80</sup> The effect of altered pharmacokinetics of many of these drugs is difficult to detect in critically ill patients. For feed-intolerant patients already receiving macrolide therapy (eg, azithromycin), there is no evidence to guide the use of additional low-dose erythromycin for prokinetic effect. In practice, we remain cautious about the synergy of macrolides and potential for adverse events, and tend to avoid using erythromycin in these patients.

Attenuation of the prokinetic effect over time may also limit the clinical usefulness of erythromycin.<sup>56</sup> The mechanisms underlying this attenuation are unclear, but it may relate to downregulation, desensitization and endocytosis of motilin receptors.<sup>81,82</sup> Because of the rate of tachyphylaxis, duration of treatment remains uncertain. During clinical trials, our group has continued prokinetic therapy for 7 days. However, many clinicians may elect to discontinue prokinetic therapy as soon as feeding has been tolerated for between 24 and 48 hours. Intuitively, this is a reasonable approach, although it may result in more patients having relapses of feed intolerance. If early discontinuation of therapy is preferred, we suggest auditing relapse rates against those published for the 7-day regimen.

Although erythromycin accelerates gastric emptying, it has been reported to slow intestinal transit.<sup>83,84</sup> However,

this may not be of major importance as a prolongation of transit is likely to increase absorption.<sup>83</sup> Diarrhoea occurs in up to 50% of critically ill patients receiving erythromycin,<sup>38,85</sup> but it is unclear whether erythromycin is the cause.

Erythromycin is the most effective prokinetic currently available for treatment of feed intolerance in the critically ill.<sup>37,68,86</sup> However, the optimal dose and dosage intervals are as yet uncertain. Based on current evidence, an intravenous dose of 70–200 mg twice daily is suggested. As concerns remain over the cardiac toxicity of erythromycin and its potential to induce microbial resistance, other agents continue to be investigated.

### Combination prokinetic therapy

As a single agent, erythromycin appears to be the prokinetic of choice for the critically ill population,<sup>37,68,86</sup> but tachyphylaxis potentially limits its effectiveness in the longer term. A single-centre study showed that a regimen combining metoclopramide and erythromycin is more effective and associated with less tolerance to the effect than the use of either drug as a single agent.<sup>37,68</sup> It is unclear whether improved feed tolerance was due to additive or synergistic effects of the drugs. Based on this evidence, a suggested protocol would be to commence intravenous erythromycin 70–200 mg twice daily plus metoclopramide 10 mg four times daily when a large GRV is noted (Figure 2).

### Potential future therapies

#### Opioid antagonists

Systemic opiates, acting via the  $\mu$  receptor, delay gastric emptying and intestinal transit.<sup>87-89</sup> Delayed gastric emptying is common in ICU patients who receive opiates for analgesia or sedation,<sup>90</sup> and  $\mu$ -receptor antagonism is expected to accelerate gastric emptying in the critically ill. Intravenous naloxone attenuates the inhibitory effect of morphine on the motility of both the oesophagus and the stomach in health,<sup>91</sup> but an opiate antagonist would need to be either minimally absorbed or not cross the blood–brain barrier to be useful in ICU patients. Meissner and colleagues reported improved feed tolerance, and fewer cases of ventilator-associated pneumonia, when 8 mg naloxone was given enterally every 6 hours to critically ill patients receiving concurrent intravenous fentanyl.<sup>92</sup> Patient selection did not depend on success of feeding, so the importance of this finding for patients intolerant of enteral nutrition is unclear. However, the findings are of interest, and further studies examining the effect of enteral naloxone in feed intolerance are required.

Opioid antagonists that act exclusively on peripheral  $\mu$  receptors are currently under investigation. These agents do

not cross the blood–brain barrier, and hence do not interfere with the required analgesic effect of opiates. Alvimopan and methylalntrexone are two promising drugs in this class. The peripheral  $\mu$ -receptor antagonists reduce the frequency of postoperative ileus<sup>93</sup> and the time to defecation in outpatients with bowel dysfunction secondary to chronic opioid use, without compromising analgesia.<sup>94,95</sup> These effects are likely to be due to acceleration of intestinal transit.<sup>96</sup> In addition, methylalntrexone has been reported to decrease GRV and improve feed tolerance in a critically ill patient.<sup>97</sup> In the United States, the Food and Drug Administration recently granted approval for in-hospital therapy with oral alvimopan in postoperative patients after partial large- or small-bowel resection.<sup>98</sup> In Australia, neither drug has yet been approved by the Therapeutic Goods Administration. Cardiac adverse events have been reported with the use of alvimopan.<sup>94</sup> Investigation of peripheral  $\mu$ -receptor antagonists as therapy in feed-intolerant patients who require opiate analgesia is warranted.

#### Motilin agonists without antibiotic activity

As noted above, erythromycin is an effective prokinetic but is limited by a number of potential problems. Although not yet proven clinically, there is significant concern that the use of small doses of erythromycin may induce antibiotic microbial resistance. Motilin agonists without antibiotic effect could provide prokinetic effect without this risk. However, to date, the development of drugs in this class has been disappointing,<sup>99-101</sup> with the lack of efficacy probably related to tachyphylaxis.<sup>81</sup> However, mitemincal an orally active motilin agonist, accelerates gastric emptying in ambulant patients with gastroparesis,<sup>102</sup> and its use as prokinetic therapy in the gastroparesis of critical illness should be investigated.

#### Alternative dopamine antagonists

Domperidone is a peripherally acting dopamine D<sub>2</sub>-receptor antagonist that affects oesophageal, gastric and small intestinal motility.<sup>103</sup> It is as effective as metoclopramide for symptom relief in gastroparesis, and is associated with fewer and less severe drug-induced movement disorders in ambulant patients.<sup>104</sup> An oral dose of 10 mg provided similar symptomatic improvement to metoclopramide and cisapride in patients with diabetic gastroparesis.<sup>103</sup> Because very little of the drug crosses the blood–brain barrier, central nervous system adverse effects are rare. This provides a theoretical advantage for domperidone over metoclopramide. Domperidone reduces gastrointestinal symptoms after acute myocardial infarction,<sup>105</sup> but has not been studied in the intensive care setting. The intravenous formulation has not been marketed in Australia because of case reports of ventricular arrhythmias and sudden death. The lack of an intravenous

formulation and the potential for cardiac adverse events limit the drug's appeal to the intensivist.

### Ghrelin

Ghrelin is structurally and functionally related to motilin<sup>106</sup> and, when given as an exogenous peptide, accelerates gastric emptying.<sup>107-109</sup> Ghrelin is also a ligand for the growth hormone secretagogue receptor.<sup>109,110</sup> Critically ill patients have reduced blood ghrelin concentrations,<sup>111</sup> but the impact of this on gastric emptying is not yet known. No studies have examined the effect of exogenous administration of ghrelin to critically ill patients. However, ghrelin has been given to patients with cachexia and chronic organ failure with interesting results; patients with chronic obstructive pulmonary disease showed increases in muscle strength and distance walked in 6 minutes,<sup>112</sup> and those with chronic heart failure showed increased left ventricular ejection fraction and exercise capacity.<sup>113</sup> The suggested mechanism is via increased food intake and muscle strength. The effect of ghrelin in treating gastroparesis in the critically ill, and thereby strengthening muscles of respiration, warrants investigation. However, the use of exogenous ghrelin may cause unwanted hyperglycaemia via the growth hormone effect.<sup>114</sup> The administration of large doses of growth hormone to patients with severe sepsis increased mortality and morbidity,<sup>115</sup> possibly because of uncontrolled hyperglycaemia. Clinical trials of ghrelin as therapy to improve feed tolerance must be designed to minimise hyperglycaemia.

### Cholecystokinin antagonist

Cholecystokinin (CCK) is released from the duodenum and jejunum,<sup>116</sup> and has multiple gastrointestinal effects, including deceleration of gastric emptying.<sup>117-119</sup> Dexloxiglumide is a selective and highly potent CCK1-receptor antagonist, which accelerates gastric emptying in animals<sup>120</sup> and humans.<sup>121,122</sup> It has been used safely, but with variable success, at a dose of 200 mg 8-hourly in patients with irritable bowel syndrome<sup>121</sup> and functional dyspepsia.<sup>120</sup> CCK is an important mediator of delayed gastric emptying in critically ill patients,<sup>35</sup> suggesting dexloxiglumide has potential to be an effective treatment in these patients.

### 5HT<sub>4</sub> agonists

Serotonin (5-hydroxytryptamine) stimulates motility via the 5HT<sub>4</sub> receptor. Tegaserod, a serotonin partial agonist, improves symptoms for patients with constipation-predominant irritable bowel syndrome.<sup>123</sup> In addition, clinical improvement was reported in an audit of critically ill patients with persistent feed intolerance.<sup>124,125</sup> Reports of drug-associated ischaemic colitis<sup>126-129</sup> and an increase in ischaemic cardiovascular events has resulted in tegaserod

being withdrawn from the market.<sup>130</sup> The implications for use of tegaserod in critical illness are unclear, but are likely to limit its application in the immediate future.

### Neostigmine

Cholinesterase inhibitors, such as neostigmine, increase availability of acetylcholine at neuromuscular junctions. In the gastrointestinal tract, increased concentrations of acetylcholine at the neuromuscular junction increase contractility and hence the speed of intestinal transit.<sup>131</sup> A trend to accelerate gastric emptying and improved feed tolerance occurred in a pilot study of neostigmine infusions in critically ill patients,<sup>132</sup> and further research into the effects of neostigmine on feed tolerance in the critically ill is indicated.

### Other techniques to improve feed delivery in the critically ill

Implementation of a feeding protocol improves delivery of enteral nutrition, but the effect on clinical outcomes (such as mortality and length of stay) has been inconsistent.<sup>13,133,134</sup> There are at least two possible reasons. Firstly, there are still many unanswered questions about the optimum method of feeding the critically ill. Issues of route and when to commence feeding have not been adequately addressed in large multicentre trials.<sup>135</sup> In addition, there is no consensus on the most appropriate treatment for feed intolerance.<sup>1,13,86</sup> Thus, feeding protocols are likely to be flawed because they are based on inadequate evidence. Secondly, the question of "amount" is pivotal to this discussion, and methods derived to determine nutrient targets are not based on clinical outcome studies.<sup>136</sup> Therefore, improving nutritional delivery by any means, whether the administration of prokinetics or the implementation of feeding protocols, may not improve, and could worsen, clinical outcomes. All treatment modalities, including nutrient delivery targets and the use of prokinetic drugs, should eventually be subjected to clinical trials powered to determine effect on mortality.

### Conclusions

The enteral route is the preferred route for delivering nutrition to the critically ill. However, many patients remain intolerant to gastric feeding, with the predominant mechanism being delayed gastric emptying. This may lead to under-nutrition and increase gastro-oesophageal reflux. Gastric emptying in the critically ill is delayed because of impaired function of the proximal and distal stomach and pylorus, as well as disordered activity in the duodenum. Drug therapy to accelerate gastric emptying can improve the delivery of enteral nutrition.



Currently, combination therapy (intravenous erythromycin 200 mg twice daily and metoclopramide 10 mg 6-hourly, for 7 days) is the most effective drug therapy for feed intolerance. This regimen may increase the incidence of diarrhoea. It also has the potential to promote bacterial resistance, although this has not been demonstrated, and its clinical importance is unclear. Other side effects, such as movement disorders, prolongation of the QT interval and drug interactions may be under-reported. Given the limitations of current feed-intolerance regimens, the search for effective, well tolerated prokinetics should continue. Future therapies may include non-antibiotic motilin agonists, opioid and CCK antagonists, neostigmine and exogenous ghrelin. Additional information is required before studies involving tegaserod are performed.

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